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Progress and Hurdles to a Safe and Effective Zika Vaccine

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21 June 2018

gdac
GLOBAL DENGUE+AEDES-TRANSMITTED DISEASES CONSORTIUM

Zika background & vaccines

- After the WHO declaration of ZIKV as Public Health Concern of International Concern in Feb. 2016, numerous manufacturers/investigators expressed interest in the development of a ZIKV vaccine
- ZIKV, like YFV, is thought to exist as a single serotype
  - Single vaccine should protect
- ZCS observed in babies born to women with and without symptomatic ZIKV illness
  - Even very low titers of ZIKV could result in ZCS – must prevention of infection, not just illness be the goal of vaccination?
- What is the ultimate target population of vaccination?
  - Pregnant women
  - Women of child-bearing age
  - Men and women
- Guillain-Barré syndrome linked to ZIKV epidemic in Latin America
  - Unclear if GBS and GBS-like syndrome was direct viral effect or immune-mediated
  - If immune-mediated, may be a concern for vaccines

ZIKV vaccines

	Developers	Type of vaccine	Antigen	Development/Phase	Registration No.
GLS-5700	GeneOne / Inovio	DNA	prM & E	Phase 1	NCT02809443 NCT02887482
VRC ZIKV DNA	VRC/NIAID	DNA	PrM & E	Phase 1	NCT02840487 NCT02996461
	BioManguinhos/ Fiocruz	VLP	E protein	Non-clinical	
ZIKVLP	Institut Pasteur Shanghai	VLP		Non-clinical	
	NewLink Genetics	VLP	PrM & E	Non-clinical	
	Bharat	PIV	Whole virus	Non-clinical	
	BioManguinhos/ Fiocruz	PIV	Whole virus	Non-clinical	
Butantan ZIKV	Butantan	PIV	Whole virus	Non-clinical	
	NewLink Genetics	PIV	Whole virus	Non-clinical	
	Valneva	PIV	Whole virus	Non-clinical	

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ZIKV vaccines (con't)

	Developers	Type of vaccine	Antigen	Development/Phase	Registration No.
ZIKV PIV	WRAIR/Harvard/ NIAID/Sanofi Pasteur	PIV	Whole virus	Non-clinical	NCT02952833 NCT02937233 NCT03008122 NCT02963909
Butantan attenuated ZIKV	Butantan	LAV	Whole virus	Non-clinical	
rZIKV/DEN2Δ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
rZIKV/DEN4Δ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
rZIKV-3′/DEN4Δ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
rZIKVΔ30	NIAID Intramural	LAV	Whole virus	Non-clinical	

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ZIKV vaccines (con't)

	Developers	Type of vaccine	Antigen	Development/ Phase
	BioManguinhos/Fiocruz	Recombinant viral vector	PrM/E & NS1 proteins	Non-clinical
	BioManguinhos/Fiocruz	Recombinant viral vector	E protein	Non-clinical
GEO-ZM05	GeoVax/ UGA/CDC	Recombinant viral vector	PrME+NS1	Non-clinical
NI.LV-ZK	Institut Pasteur France	Recombinant viral vector	PrM/E	Non-clinical
ChAdOx1-Zk	Zika structural proteins	Recombinant viral vector		Non-clinical
Chimeravax-Zika	Sanofi Pasteur	Recombinant viral vector	Zika structural proteins	Non-clinical
SCV-CHIKV+ZIKV+YF	Sementis Ltd	Recombinant viral vector	ZIKV, CHIK, YF	Non-clinical
MV-Zika	Themis Bioscience GmbH	Recombinant viral vector	E (poss prM)	NCT02996890
VXA-Zikavax	Vaxart	Recombinant viral vector	Env+	Non-clinical
Replikins Zika Vaccine	Replikins, Ltd and LLC	Peptide	Synthetic peptides	Non-clinical
mRNA-1325	Valera (Moderna)	mRNA	prME	NCT03014089

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VRC Zika DNA vaccine

- Vaccine Research Center at U.S. NIH developing Zika DNA vaccine
- Based on DNA vaccine for WNV that demonstrated safety and immunogenicity in both younger and older individual
- Plasmid contains the coding sequences for Zika virus prM/E
- Phase 1 clinical trial has started with two constructs

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VRC DNA vaccine

- Assessed 2 constructs – one was modified such that final 98 aa of E were exchanged with corresponding JEV sequences to improve subviral particle (SVP) secretion
- Tested 1mg or 4mg doses (2 doses given 4 weeks apart)
  - Compared with a single 1 mg dose or placebo
- Challenge NHP 8 weeks after first dose
  - 17/18 animals that received 2 doses were protected

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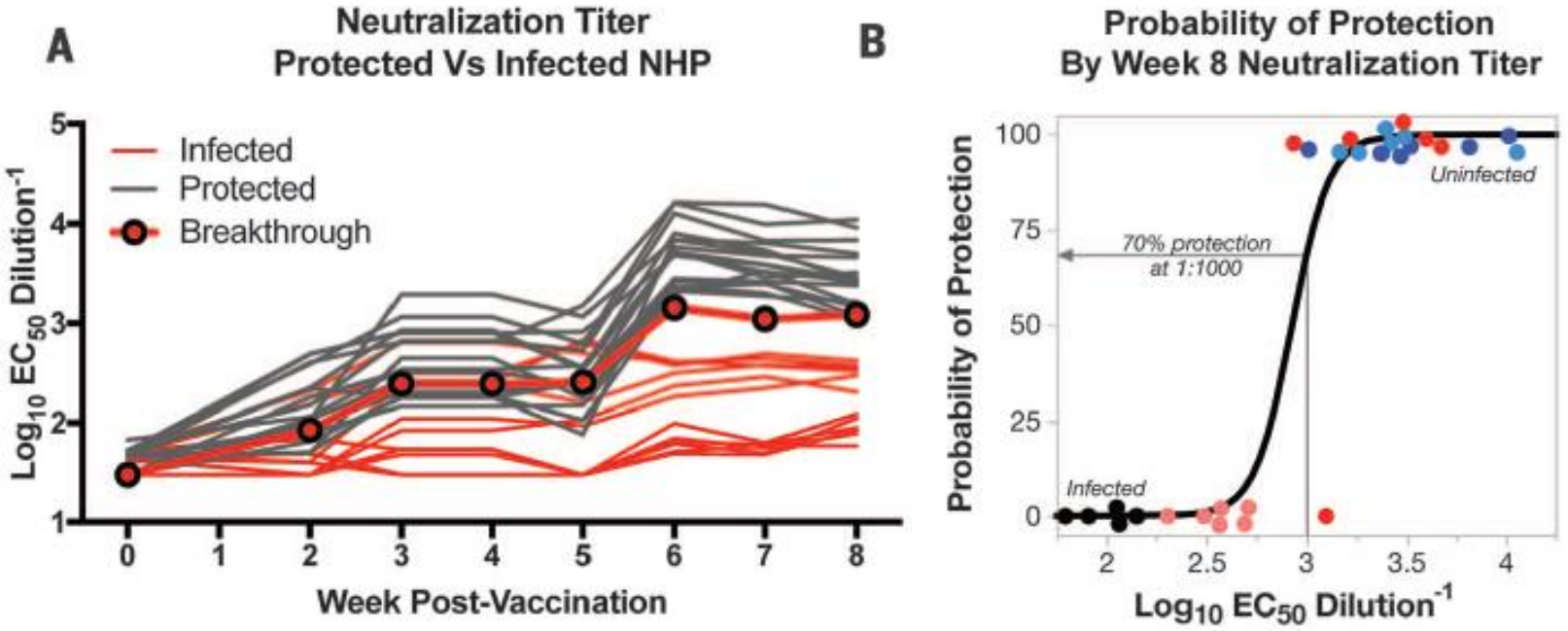
VRC DNA vaccine – protection correlates with Nab titer



Dowd, et al. Science Vol. 354, Issue 6309

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Phase I clinical trial of VRC DNA vaccine

- 2 different DNA vaccines tested:
  - VRC5283 : E region contains wild-type Zika virus sequences
  - VRC5288: chimeric E region in which the stem and TM regions are made up of JE sequence
- VRC 319 received VRC5288
  - Group 1 received 4mg on weeks 0 & 8
  - Group 2 received 4 mg on weeks 0, 12
  - Group 3 received 4 mg on weeks 0, 4, & 8
  - Group 4 received 4 mg on weeks 0, 4, and 20
- VRC 320 received VRC5283 received 4 mg at 0, 4, & 8 wks
  - Group 1 received vaccine 4 mgs IM
  - Group 2 received 2mg IM in each deltoid (total 4mg)
  - Group 3 received split dose (2mg) into each deltoid, given by syringe and needle-free device

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Gaudinski, et al The Lancet, 2017

EC_{50} titers (flow-based assay using RVPs)

		First vaccination		Second vaccination		Third vaccination	
Study group	Baseline GMT	GMT at 4 wk post	% responder	GMT at 4 wk post	% responder	GMT at 4 wk post	% responder
VRC 319							
Grp 1	16.3	35.1	45%	67.3	60%	N/A	N/A
Grp 2	16.2	35.1	55%	55.4	75%	N/A	N/A
Grp 3	16.1	27.4	35%	41.9	60%	80.5	80%
Grp 4	16.5	36.9	50%	40.5	65%	120.3	85%
VRC 320							
Grp 1	19.5	20.9	13%	26.4	29%	47.8	77%
Grp 2	17.8	36.9	40%	100.8	73%	149.7	93%
Grp 3	15.8	96.2	86%	319.2	100%	304.3	100%

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VRC ZIKV DNA vaccine

- VRC320 construct was chosen to move forward in Phase 2b clinical trial to evaluate efficacy
- Phase 2 clinical trial sites:
  - US
  - Brazil
  - Puerto Rico
  - Colombia
  - Mexico
  - Panama
  - Peru
- Unclear if efficacy endpoint can be met

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Inactivated Zika vaccine

- Purified inactivated virus (PIV) vaccine developed from Zika virus Puerto Rico strain
- 1 µg of PIV vaccine with alum administered by the i.m. route completely protected Balb/c mice from challenge with ZIKV-BR at 4 weeks
  - PIV administered by the s.q. route did not protect 100% of mice
    - Non-protected mice showed low-level viremia (lower than sham vaccinated mice)

Larocca, et al, Nature, June 26 2016

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Phase I clinical trial

- Participants were enrolled at WRAIR, SLU, and BIDMC
  - WRAIR participants were screened with microneut, SLU by MAC ELISA; BIDMC did not screen (used history only)
- 67 participants randomized to receive vaccine (55) or placebo (12) (open-label)
- Different dosing regimes evaluated
  - WRAIR assessing effect of pre-existing antibody (YF vaccine or JE vaccine followed by ZPIV
  - SLU evaluating 5mg, 2.5mg and 10 mg dose given 4 weeks apart
  - BIDMC evaluating 2 doses (5mg given 4 weeks apart or 2 weeks apart, or one dose

Antibody response

$PRNT_{50}$ (by microneutralization assay)				
Study Day	**WRAIR (n=20)**	**SLU (n=25)**	**BIDMC (n=10)**	**ALL (n=55)**
Day 29	8.5 (4.7 – 15.3)	5.5 (4.5 – 6.8)	8.7 (2.5 – 30.4)	7.0 (5.2 – 9.5(
Day 57	100.8 (39.7-255.7)	142.9 (70 – 290.4)	820.6 (357-1885.8)	437.9 (245.7-286.5)
Peak titer after 2nd dose	100.8 (39.7-255.7)	345.6 (166.4-718)	1061.7 (425.8-2489)	286.7 (170.6-481.6)

Of 52 participants with data available after the second dose, 48 (92%) seroconverted defined as titer ≥ 10; 40 (77%) seroconverted defined as titer ≥ 100

Modjarrad, the Lancet, 2018

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Conclusions

- Two doses of the purified inactivated vaccine induced neutralizing antibodies at a titer of ≥ 1:100 in 77% of vaccinated individuals
- Passive transfer of vaccine-induced antibody at a MN_{50} of ≥ 1:100 protected mice from challenge with wt ZIKV
- Originally planned to evaluate a third dose of vaccine
- Development program on hold for now

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Zika virus cases in the United States and U.S. territories 1/1/15-12/19/17)

United States		U.S. Territories	
Travel Associated	Locally-acquired (vector-borne)	Travel Associated	Locally-acquired (vector-borne)
5,335	227	147	36,956
Total	**5,615[1]**	**Total**	**37,103[2]**

United States		U.S. Territories	
Completed pregnancies	2,143	Completed pregnancies	3,738
Live born with birth defects	102	Live born with birth defects	142
Pregnancy losses with birth defects	9	Pregnancy losses with birth defects	8
Sexually-transmitted	49[3]	Sexually-transmitted	?
Guillain-Barré	13	Guillain-Barré	50

1. Includes 1 case of laboratory transmission and 1 case of unknown source
2. 98% of cases come from Puerto Rico
3. 1 case of female-to-male transmission

Source: CDC

Symptomatic ZIKV cases reported to CDC

	United States			US Territories		
	Travel associated	Locally-acquired	Total	Travel associated	Locally-acquired	Total
2017	378	3	385[1]	0	611	611
2016	4,830	224	5,102	142	35,937	36,079
2015	61	0	61	1	8	9

1. Includes 4 cases of sexual transmission
2. Includes 46 cases of sexual transmission, 1 laboratory acquired and 1 acquired through an unknown route

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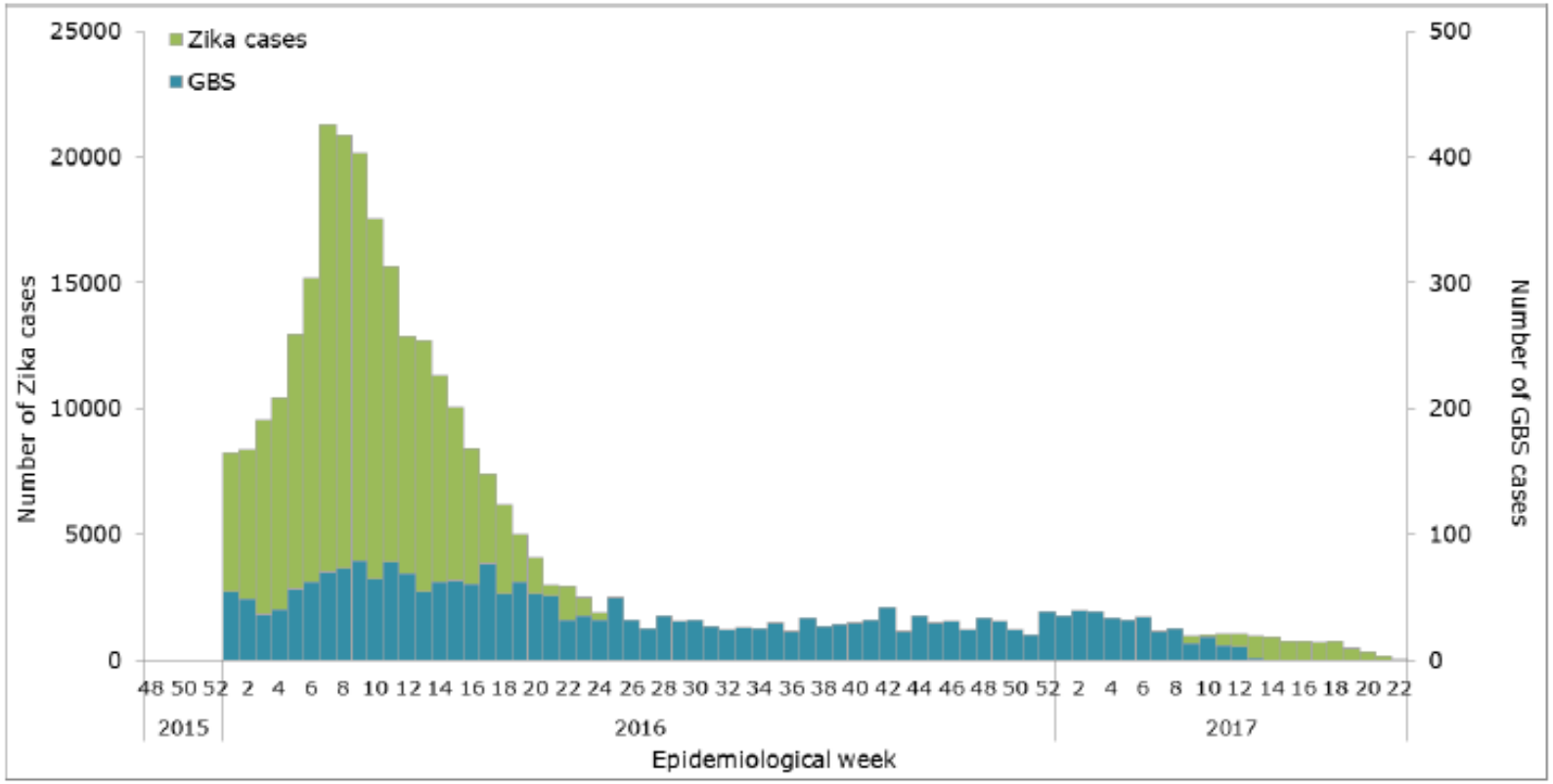
Zika cases over time - Brazil

Figure 5. Total cases of Zika and GBS by EW. Brazil. EW 1 of 2016 to EW 22 of 2017.



Source: Data provided by the Brazil Ministry of Health to PAHO/WHO[3]

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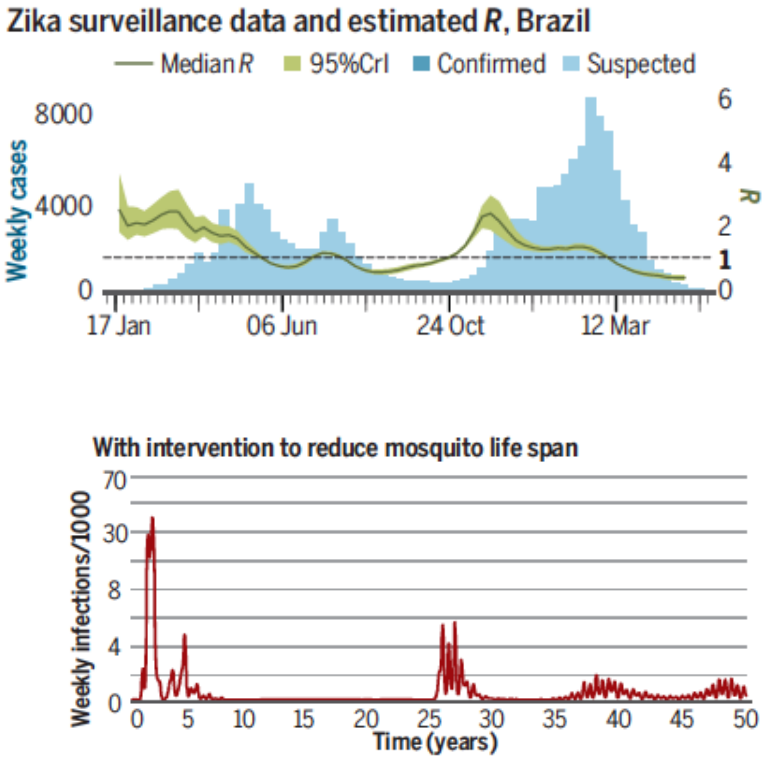
Predicted outbreaks of Zika

- Zika incidence has decreased markedly since 2015
- Ferguson, et al predicted duration of current outbreak to be 3 years
- Predicts future outbreaks every 10 years (need to replenish susceptible populastion



Ferguson, et al, Science, 2017

ZIKA

- Zika epidemic nearly finished in Latin America
  - Sporadic cases reported
- Asia has not yet reported any large outbreaks although ZIKV transmission has been documented
- No new cases of GBS have been reported due to Zika
- Phase 3 efficacy studies may be impossible if outbreak wanes – STAY TUNED
  - Phase 2b study of VRC DNA scheduled has started in Latin America

What is the regulatory pathway forward?

- Technical consultation on immune correlates of ZIKV was held at the NIH March 7 – 8
  - WHO, NIH, and FDA
- FDA expressed openness to use of a ZIKV challenge model as a pathway to licensure if traditional Phase 3 efficacy studies could not be done
- Other considerations included use of a known correlate of protection to bridge to licensure, possible use of the Animal Rule however this was less acceptable

ZIKV Controlled Human Infection Model

- First proposed in mid-2016 as tool to down-select the more than 40 candidate vaccines proposed
- Ethics consultation held in December of 2016
  - Data were not presented on sexual transmission cases (number of cases, interval from return from endemic area, association with symptoms, etc)
  - Data were not presented on prospective studies ongoing of GBS
  - Committee was not experienced with the use and conduct of human challenge studies
- The committee did not review or ask about the planned CHIM protocol

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Conclusions from an ethical review of Zika human challenge convened by US NIH December 2016

https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf

Key Question: Are the **risks reasonable, minimized, and justified** by the potential **social value** of the trial?

Conclusion:

- There is substantial uncertainty about the risks to potential volunteers in Zika virus human challenge study.
- Particular concern about possible risks to third parties (foetuses, members of the community)
- Absence of a strong argument and evidence that a challenge study will accelerate vaccine development
- Absence of an indication that field trials will be prohibitively difficult to conduct
- The committee concluded that it is premature to proceed with a Zika virus human challenge trial

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What has changed?

- It is clear that the epidemic has waned and traditional Phase 3 efficacy studies will not be possible
- There are substantial data on the clinical course of ZIKV infection in humans
- Third party protections can be put in place
- ZIKV CHIM can provide data on shedding of virus and its relation to symptoms that natural infection studies have not provided
  - Peak titer in blood and relation to shedding
  - Duration of shedding in multiple body fluids
  - Titer of virus and symptoms
- Recent data demonstrate low frequency of shedding of ***infectious virus*** in semen

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Infectious ZIKV in semen

- Overall, 60/186 (33%) of men had a semen sample positive for ZIKV by RT-PCR ***but***
- 22/36 (61%) who submitted a sample between 14 – 30 days after symptom onset were positive
- 78 samples that were positive by RT-PCR were tested by culture
  - Only 3 samples (4%) contained infectious ZIKV
  - These samples were collected within 30 days of symptom onset
  - All had viral load by RT-PCR of ≥ 7 $\log_{10}$ RNA copies/mL

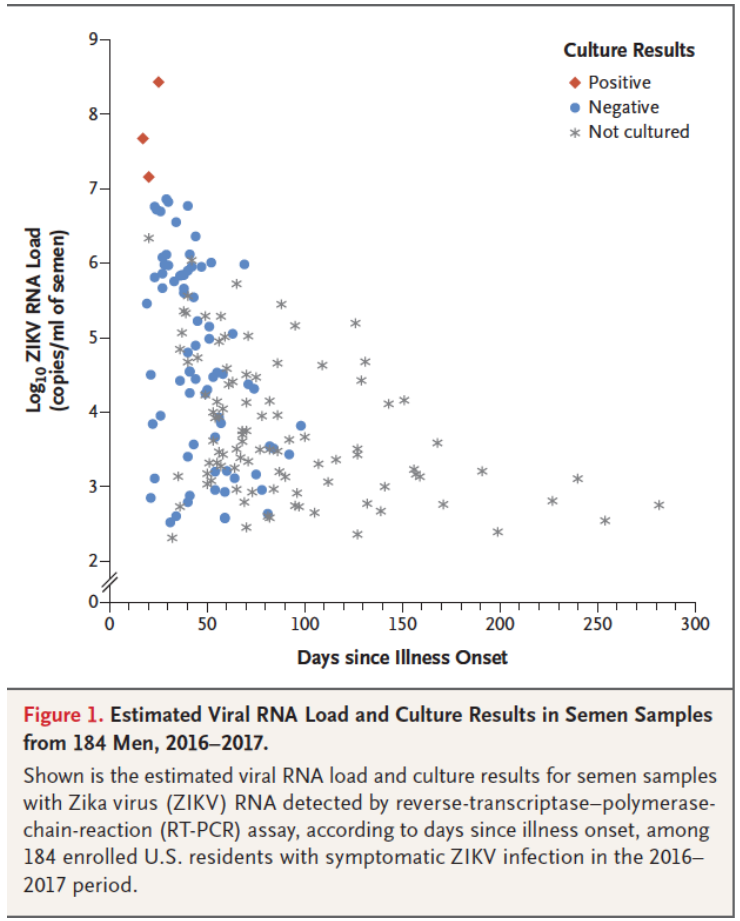

Figure 1. Estimated Viral RNA Load and Culture Results in Semen Samples from 184 Men, 2016–2017.

Shown is the estimated viral RNA load and culture results for semen samples with Zika virus (ZIKV) RNA detected by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, according to days since illness onset, among 184 enrolled U.S. residents with symptomatic ZIKV infection in the 2016–2017 period.

Mead, et al, NEJM, 4/12/18

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Sexual transmission of ZIKV

- The culture data correlate with the epidemiologic data of sexual transmission:
- All but one case have occurred within 21 days after illness onset in the source male patient (one have occurred at day 41)
  - Infectious virus was detected in semen only in samples collected within 30 days of return from endemic area
  - Infectious virus was detected only in samples with high viral load (>7 $\log_{10}$)
- Men who were older and ejaculated less frequently were more likely to have prolonged shedding in semen than younger men who ejaculated more frequently (flush the virus out?)
- May be able to identify subjects at risk for transmitting ZIKV sexually by determining viral load.

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Conclusions

- Awaiting the results of the Phase 2b trial of the VRC ZIKV candidate DNA vaccine VRC320 and the Moderna mRNA vaccine trial (Phase I)
- Other manufacturers are waiting to see if Zika will re-emerge – most programs currently on hold
- Reduced transmission of ZIKV makes traditional Phase 3 efficacy trial unlikely – may require alternative pathway for licensure
  - Stay tuned for more discussion